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Molecular networks in dynamic multilevel systems

A. Gastón Orrillo, Andrea M. Escalante, Maitena Martinez-Amezaga, Ignacio Cabezudo and Ricardo L. E. Furlan*[a]

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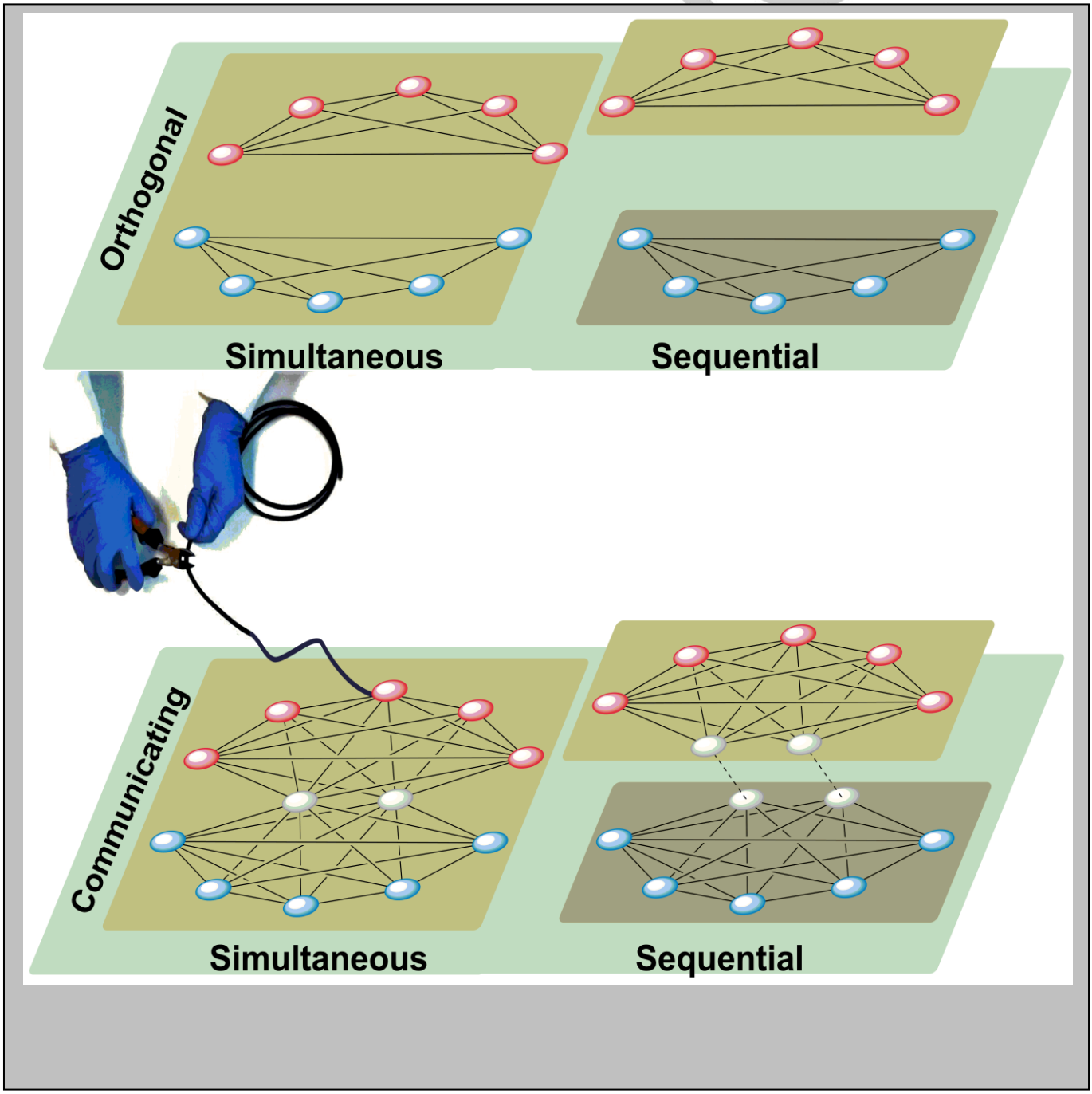

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Abstract. Dynamic multilevel systems can be assembled from molecular building blocks through two or more reversible reactions that form covalent bonds. Molecular networks of dynamic multilevel systems can exhibit different connectivities between nodes. The design and creation of molecular networks in multilevel systems require to control the crossed reactivity of the functional groups (*how* to connect nodes) and the conditions of the reactions (*when* to connect nodes). In the recent years, the combination of orthogonal or communicating reactions, which can be simultaneous or individually activated, has produced a variety of systems which gave place to macrocycles and cages, as well as molecular motors and multicomponent architectures on surfaces. A given set of reactions can lead to systems with unique responsiveness, compositions and functions, as a result of the relative reactivities. In this concept article, different molecular networks from synthetic systems are discussed which can be produced by combinations of different reaction types. Moreover, applications of this chemistry are highlighted, and future perspectives envisioned.

Dynamic covalent chemistry gives access to systems that are responsive in nature. Their molecular composition can change in response to specific stimuli that affect the constituents relative stability.[1] Such adaptation involves changes in noncovalent interactions within the system, which can induce changes in the molecular composition. Therefore, adaptation is the result of the interplay between a dynamic molecular network and its supramolecular counterpart.[2]

The dynamic covalent chemistry used for the preparation of a dynamic system will define the connections between the nodes of the network.[2c,3] In this context, molecules can be represented as network nodes whereas the reversible reactions that interconvert those molecules are the connections. When two or more reversible reactions are used in one dynamic system, the relative reactivity of the different functional groups involved will affect the wiring of the molecular network, and consequently its adaptability.

Orthogonal versus communicating reactions and their networks

In the context of dynamic covalent chemistry, reversible reactions are considered orthogonal when they do not interfere with each other,[4,5] i.e. each reactive functional group is involved in the formation of only one type of covalent bond. Dynamic systems based in two orthogonal reactions can be represented as two independent molecular subnetworks (Figure 1a).

Alternatively, two reversible reactions can communicate to each other when some of the reactive functional groups participate in the reversible formation of more than one type of covalent bond.[1d,6] The molecular subnetworks of dynamic systems based in two communicating reactions are connected through those nodes that include the functional group that can participate in both reactions (Figure 1b).

Communication and orthogonality are characteristics that are independent of the exchange activation/deactivation timing. Depending on their intrinsic reactivity and the medium, two reversible reactions, either orthogonal or communicating can be activated simultaneously or they can be activated individually at different times, leading to activation/deactivation sequences.

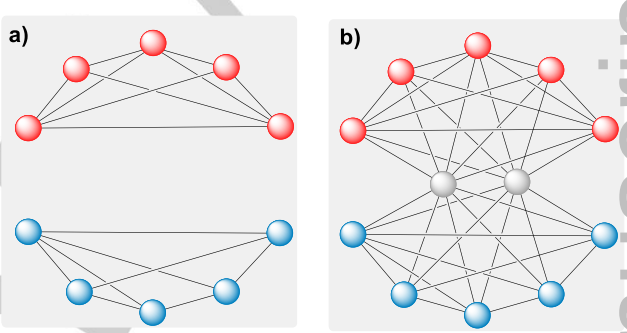

Figure 1. Molecular networks of multilevel dynamic systems obtained by combining two (a) orthogonal or (b) communicating reactions.

Multilevel dynamic systems based in Orthogonal Reactions

Simultaneous one-pot setting

Some pairs of orthogonal reversible reactions, which can be simultaneously activated, are disulfide and boronic ester exchanges,[7] disulfide and hydrazone[8] or imine[9] exchanges, and imine exchange and olefin metathesis.[10]

One recent example of a three dynamic covalent reaction system was reported by Anslyn and co-workers, who studied the reversibility and orthogonality of simultaneous hydrazone exchange (compounds **1**-**8**), thiol addition to conjugate acceptors (compounds **9**-**16**) and boronic ester exchange (compounds **17**-**24**, Figure 2).[11] Under appropriate conditions (3:1 CD_3OD/HEPES, pH = 7.4), all the three reactions can proceed without chemical interference, giving place to a set of three isolated subnetworks with identical network structures (Figure 2).

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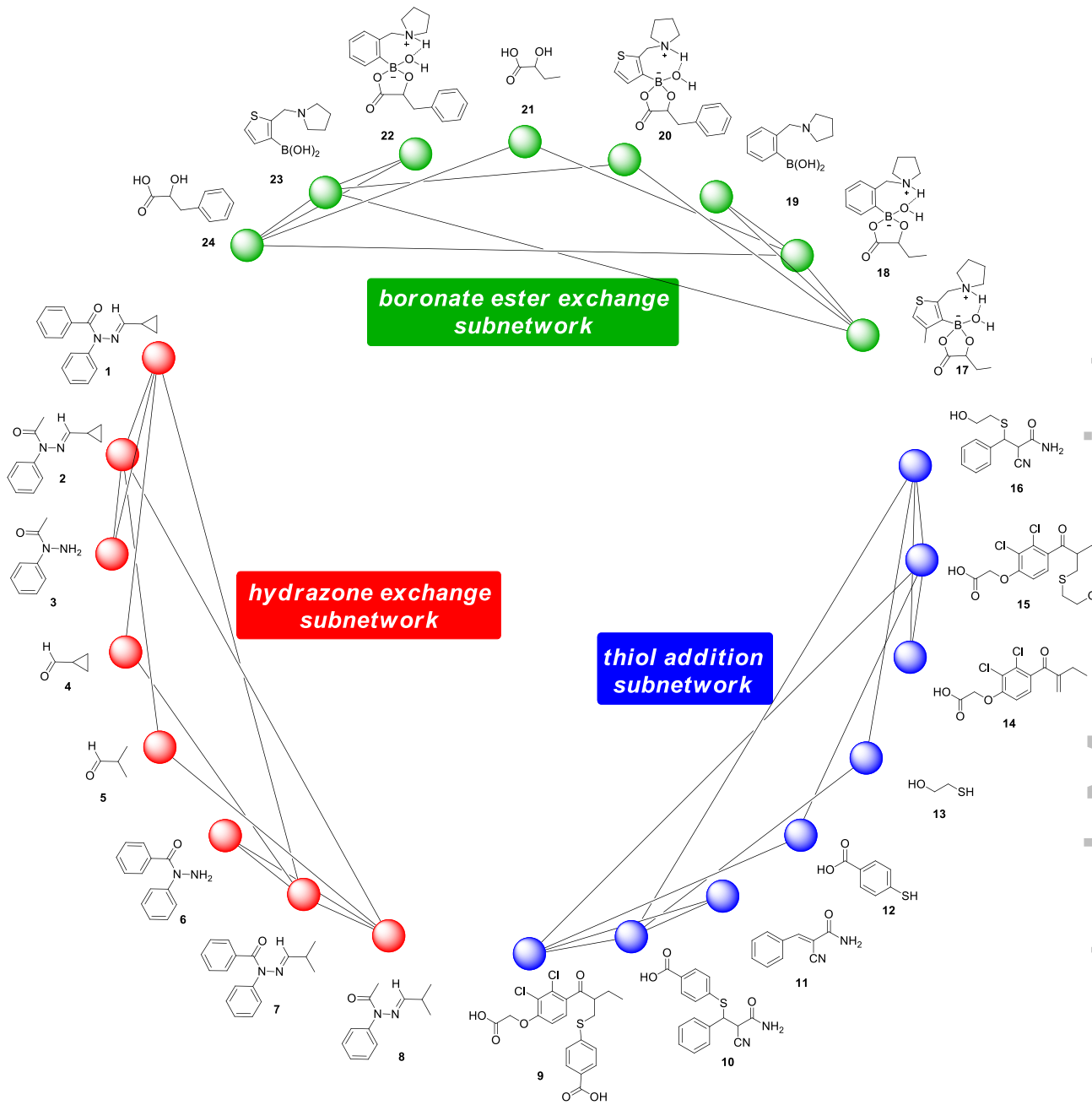

Figure 2. Molecular subnetworks generated in a dynamic multilevel system prepared through orthogonal and simultaneous boronic ester exchange, reversible thiol addition and acyl hydrazone exchange. Reaction conditions: 3:1 CD_3OD/ HEPES (pH = 7.4).

Molecular subnetworks of simultaneous-orthogonal reactions can be connected to each other if some of the molecules (nodes) are ditopic —i.e., they include two functional groups that can participate, individually, in different orthogonal reactions. In the presence of a template, this type of molecular networks can express one supramolecular library member that is produced by the activity of both orthogonal reactions, in addition to noncovalent interactions. In an early example, Otto and Nitschke combined simultaneous formation and exchange of imines and disulfides by the reaction of **25** and **26** with 2-formylpyridine **27**. Although in principle, a mixture of homo and heterodisulfides, containing one, two or no imine bonds, could be generated, only three of them, **25**, **26** and **28,** were detected. The rest of the library stayed as virtual library members, resulting in a minimalistic network (**29**-**31**, Figure 3a).[9] In the presence of a metal, the equilibrium was shifted towards imine and disulfide-containing products (Figure 3b). Supramolecular interactions involving different metal templates favoured the amplification of **30**: Cu^{1+} led to the amplification of the dimer **32**, whereas Fe^{2+} led to the amplification of the triple helicate **33** (Figure 3c). As a consequence of complex formation, the

molecular network was rewired to allow the amplification of the more favored components.

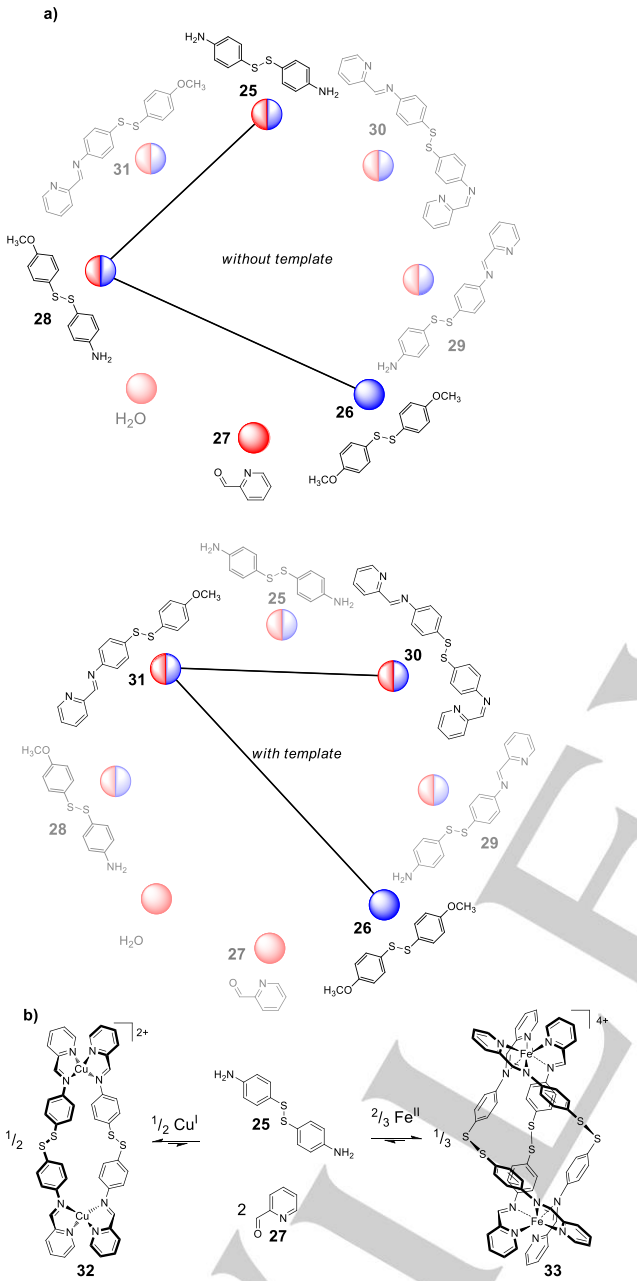

Figure 3. Molecular networks produced from building blocks **25-27** in the absence (a) or in the presence (b) of a Fe^{2+} template. Faded structures and nodes represent undetected library members (virtual members). (c) Complexes **32** and **33** formed by the addition of Cu^{1+} or Fe^{2+}. Reaction conditions: TEA, CD_3CN.

In the absence of templates, dynamic systems based on simultaneous orthogonal reversible reactions prepared from bifunctionalized building blocks can express library members in increased concentration as the result of self-sorting, as in the case of the multicomponent organic cages **34** and **35** reported by Ulrich *et al.* (Figure 4),[12] or those reported by Zhang *et al.*[10,13,14]

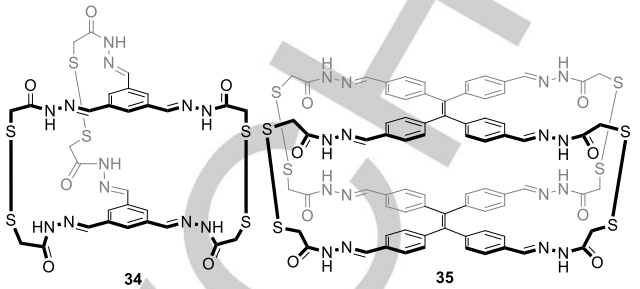

Figure 4. Molecular structure of the cages produced by self-sorting using simultaneous disulfide and hydrazone exchanges. Reaction conditions: aqueous buffer/DMSO 25/75 (v/v) (**34**) or DMSO/H_2O 94/6 (v/v) (**35**).

Orthogonal simultaneous reactions have been used for the assembly of multicomponent architectures. The lack of interference between reactions can be helpful to carry out the reactions in a spatially organized way. Bonifazi and co-workers applied simultaneous disulfide, hydrazone and boronic ester exchange to decorate a preprogrammed α-helical peptide bearing receptor sites able to react with chromophores containing the corresponding reaction partners, thiol **36**, aldehyde **37** or boronic acid **38** (Figure 5).[15] This elegant approach allowed the assembly of dyes in the desired ratio and spacing, as dictated by both the relative positioning and distribution of the recognition units on the peptide scaffold.

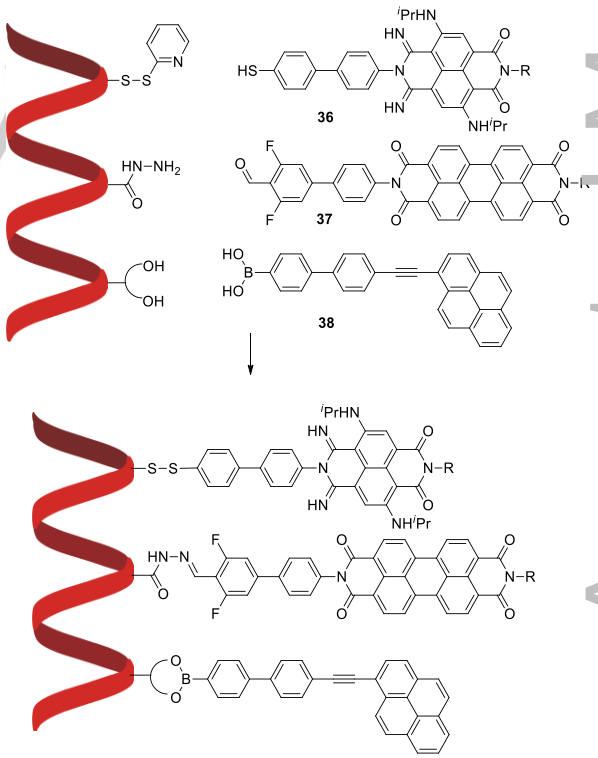

Figure 5. Simultaneous orthogonal disulfide exchange, acyl hydrazone formation and boronate formation on a peptide scaffold to produce tailored chromophores. Reaction conditions: *m*-phenylene diamine, THF.

Sequential setting

When a system includes two (or more) orthogonal reversible reactions, and the applied reaction conditions are such that each reaction can be individually activated, different activation/deactivation sequences can be designed.[16]

Although disulfides and hydrazones can be exchanged simultaneously in near to neutral aqueous media, they can be activated individually by controlling the medium acidity. The hydrazone exchange is catalyzed by acid while it is inactive or can be inactivated in a medium where an excess of base exists. In contrast, disulfide exchange is active under basic conditions but remains inactive in the presence of excess acid.[8,17] Therefore, these two exchange processes can be activated/deactivated following both possible sequences: first disulfide exchange and then hydrazone exchange and *vice versa*. The alternate activation of these two orthogonal reactions was used by the group of Leigh for the construction of one system wherein a molecule can walk up and down a molecular track. Each step given by the molecular walker is triggered by selective reaction of one foot with the appropriate reaction site positioned along the track.[18-20]

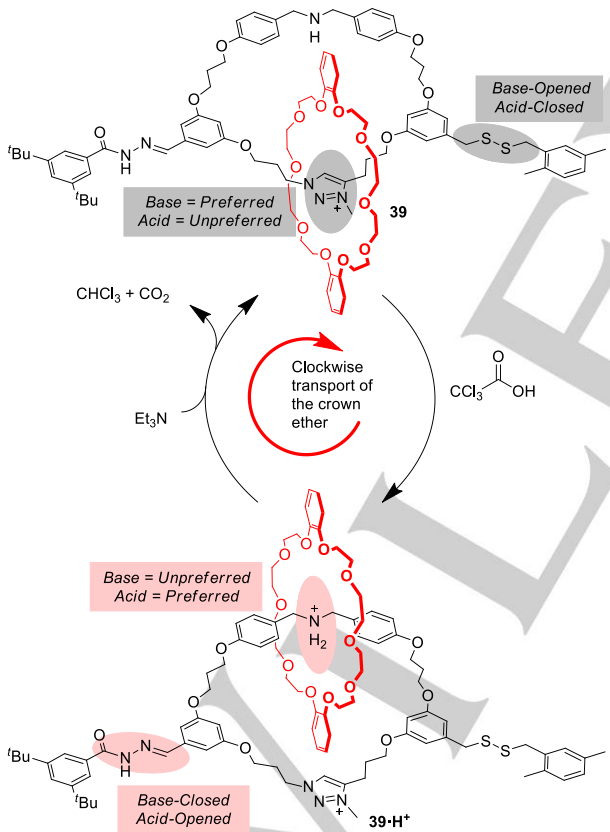

Figure 6. Operation of the rotary motor **39** using Cl_3CCO_2H as a source of chemical fuel. Reaction conditions from **39** to **39·H⁺**: hydrazide, Cl_3CCO_2H. From **39·H⁺** to **39**: thiol, disulphide, TEA. Solvent: CD_2Cl_2.

The sequential activation of two orthogonal dynamic covalent bonds can be coupled to the sequential activation of supramolecular interactions to introduce desired properties in a dynamic system. Leigh and his group recently accomplished a unidirectional molecular movement by using the [2]catenane rotary motor **39** (Figure 6).[21] A crown ether macrocycle, threaded along a circular track, was transported using acid-base oscillations to control both, the alternate opening and closing of two gates and the relative binding affinity of the macrocycle towards two binding sites positioned along the track. The gating system is based on base-labile disulfide and acid-labile hydrazone locks. While one gate is open, the movement of the macrocycle along the track is driven by its relative affinity for two binding sites: a triazolium site and a dibenzylammonium site. Acid medium selectively opens the hydrazones gate and activates the dibenzylammonium binding site. On the contrary, a base keeps closed the hydrazones gate, opens the disulfide gate and produces dibenzylammonium deprotonation, so the macrocycle moves to the now preferred triazolium binding site. The acid-base oscillations were induced by aliquots of trichloroacetic acid, in the presence of triethylamine. A single pulse of the chemical fuel can drive an autonomous clockwise 360° rotation of the crown ether along the track, converting a source of chemical energy into molecular motion.

The group of Matile added the exchange of boronic esters as a third reversible reaction that can be sequentially activated under certain conditions when combined with disulfides and hydrazones in a single system.[22] Incorporation of a third reaction increases the number of potential reaction activation/deactivation sequences. However, the lability of boronate esters under the acidic conditions required for hydrazone exchange initially imposed some sequence restrictions. Boronate esters could only be introduced into the system after the hydrazone exchange had been deactivated.[22] In order to broaden sequence flexibility, the Matile group improved the compatibility between boronate esters and hydrazones using boronate esters with increased acid stability and organocatalysis, to exchange hydrazones under moderate acid conditions.[22a] This set of conditions paved the way for the activation of hydrazone exchange in the presence of boronate esters. The three reactions were combined to build up a system by self-organizing surface-initiated polymerization and templated stack exchange by sequential activation of disulfide, hydrazone, and boronate ester exchanges. Disulfide exchange under basic conditions is used first to grow single π stacks directly on oxide surfaces. Next, hydrazone exchange under acidic conditions with **40** is used to add a second string or stack, and subsequently, boronic-ester exchange with **41** under moderately basic conditions is used to build a third one. Finally, hydrazones exchange with acetylhydrazide and catalyst **42** is activated again to liberate the intact boronate ester **43** (Figure 7).

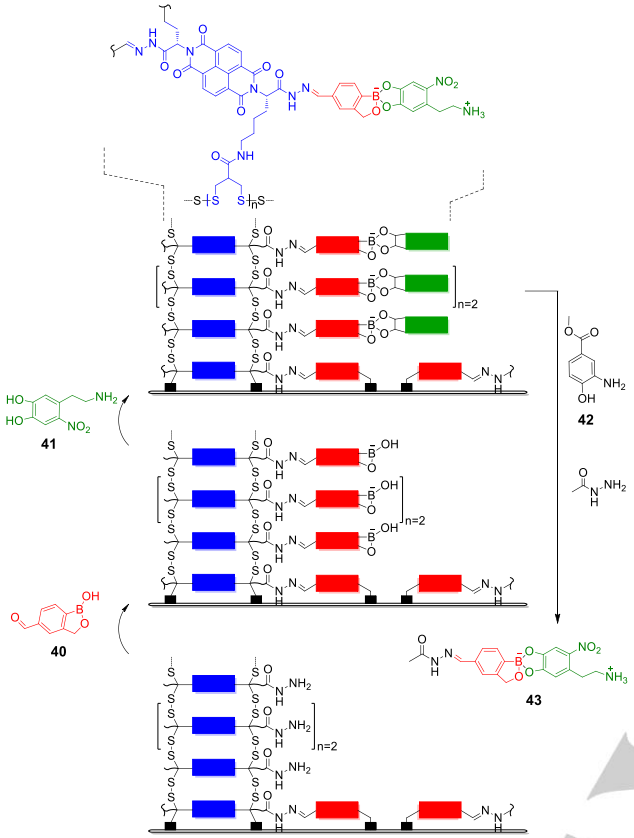

Figure 7. Sequential and orthogonal exchanges of disulfides (TEA, DMSO-d_6), acyl hydrazones (**40**, AcOH, DMSO), boronate esters (**41**, DMSO, DIPEA), and hydrazones (**42**, acetylhydrazide, TFA, DMSO-d_6).

The sequential activation of orthogonal reactions could be used to explore different regions of the chemical space. If multi-topic nodes are introduced in these types of systems, reaction sequences could be used to build up complexity on those multi-reactive entities. Thanks to the reversible chemistry used, each complexity layer could be the product of adaptation of the subnetwork that is active at that particular moment to a given stimulus.

Multilevel dynamic systems based on Communicating Reactions

The combination of exchange chemistries that can communicate with each other leads to the generation of two exchange pools that share one building block type. Therefore the two exchange pools can affect mutually as a consequence of their competence for the building block type they both have in common.

Some pairs of reversible reactions that communicate with each other are: the exchange of disulfides and thioesters,[6] dithioacetals,[23] or thio-Michael adducts,[24] the exchanges of imines and hydrazones, oximes[25] and nitrones,[26] and the exchange of nitroaldol adducts and hemithioacetals.[27]

Simultaneous one-pot setting

In a pioneering work, the group of Otto and Sanders prepared a dynamic system based on disulfide and thioester exchanges and showed how the product distribution of the thioesters pool was affected by the oxidation degree of the disulfides pool.[6] Recently, the group of Otto designed the antiparallel combination of thio-Michael addition and disulfide exchange.[24] A set of libraries was prepared where the thio-Michael acceptor **44** was added to mixtures containing the thiol **45** previously oxidized in different degrees (Figure 8a). In the fully reduced mixture, only thio-Michael adducts and thiols were present, whereas, in the fully oxidized mixture, a prevalence of disulfides formed from **45** was observed. The mixtures with intermediate oxidation levels contained thio-Michael adducts, disulfides, and species containing both types of bonds. In the networks formed at the extremes of the oxidation level (0 and 100%, Figure 8b), the low number of nodes restricts the number of edges between nodes. A different situation is observed for the networks of libraries constructed at intermediate oxidation levels (20, 50 and 80%, Figure 8). These networks have a higher number of nodes, some of which are ditopic, and a higher number of edges. The control exerted on the oxidation level of the system affects the distribution of bond types in the library and, as a consequence, the wiring of the network.

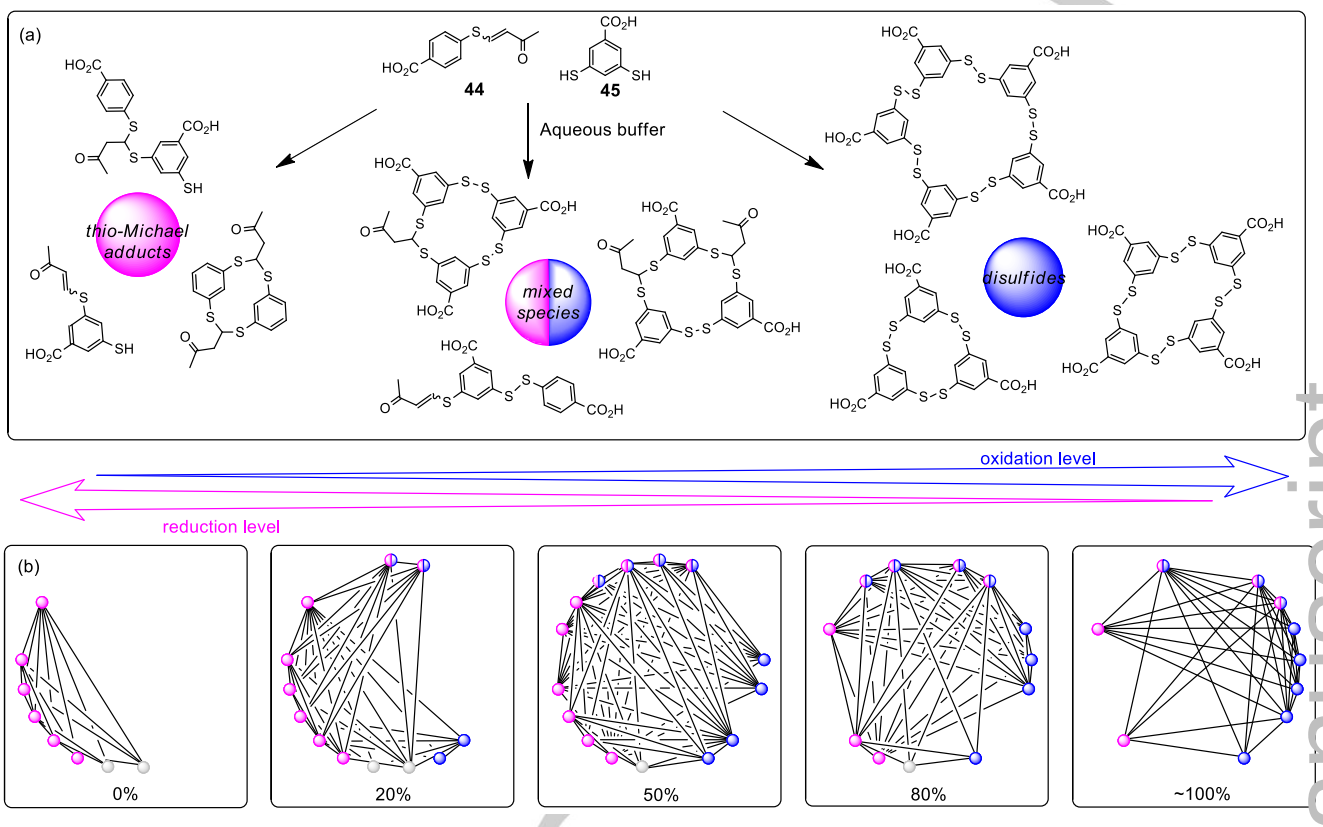

Figure 8. (a) The addition of Michael acceptor **44** to mixtures containing the dithiol **45** with different oxidation levels can lead to thio-Michael adducts (fully reduced library), predominantly disulfides (fully oxidized library) or to compounds containing dithiane and disulfide bonds (intermediate levels of oxidation). (b) The percentage associated with each network corresponds to the degree of oxidation of the thiols in the corresponding system. Grey nodes represent thi- Reaction conditions: TCEP or DTT (reducing agents added to 100% oxidized DCL), I_3^- or $NaBO_3$ (oxidizing agents added to 0% oxidized DCL), aqueous borate buffer, pH = 8.2.

Double-level fully connected systems have been coupled to irreversible transformations mediated by either biological or chemical agents, to select and withdraw compounds with a desired property from the dynamic equilibrium. The group of Ramström combined imine exchange and imine cyanation (Strecker reaction) in one system.[28] A subnetwork of twelve imines was generated by mixing equimolar quantities of imines **46**, **47** and **48**, with amine **49** (Figure 9a). Addition of TMSCN and $ZnBr_2$ activated the Strecker level leading to twelve α-aminonitriles (as the racemates) that are potential substrates for lipase-catalyzed acylation. Since both reactions are reversible and simultaneous, and they communicate with each other, the selective removal of some components by acylation can force re-equilibration of the entire system (Figure 9b). The Strecker adduct **50** was not a predominant component in the absence of the enzyme; however, it was the best lipase substrate. Therefore, in the presence of the enzyme and an acyl donor, the acylated product **51** was the main product. The system was able of asymmetric discrimination with up to 92% *ee*. Although the enzyme picks up its preferred substrates from the Strecker adducts subnetwork, it drives the adjustment of the whole network.

The same group also screened a two-level dynamic system, based on the nitroaldol reaction and hemithioacetal exchange.[29] The group of Philp assembled a dynamic system based on simultaneous interconversión of imines and nitrones.[30] In this case, the reaction network of the system was affected by the addition of a maleimide that forms a binary complex with two selected nitrones. This recognition mediates an irreversible 1,3-dipolar cycloaddition reaction which drives the resolution of the library, affecting the composition of the entire imine/nitrone system.

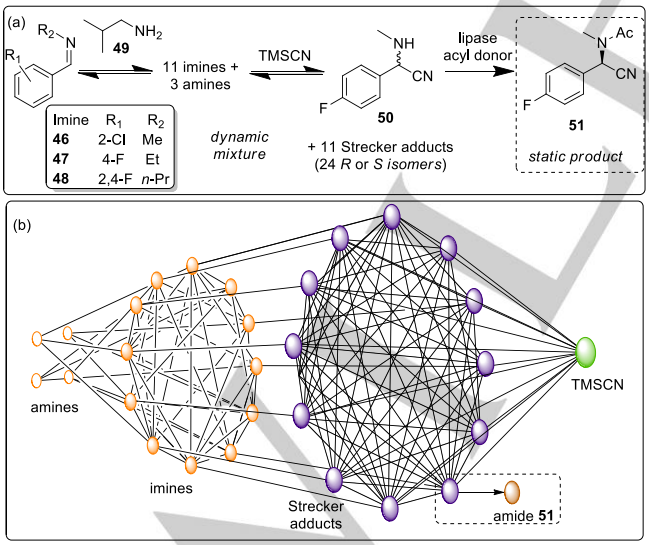

Figure 9. (a) Double dynamic multicomponent resolution system based on imine exchange ($ZnBr_2$, DMSO-d_6, benzene-d_6), the formation of Strecker adducts (TMSCN, acetic acid) and a final enzymatic step (solid $ZnBr_2$, toluene, phenyl acetate). (b) Molecular network of the system.

Sequential setting

Similarly to the sequential activation of orthogonal reactions, the sequential activation of communicating reactions can lead to some interesting properties. This type of two-level system has been prepared by the combination of dithioacetal and disulfide exchanges.[23] In the presence of acid, thiols react exclusively with dithioacetals, whereas in the presence of base they react only with disulfides. Since thiols are reactive towards both reactions, they act as connecting nodes of the two subnetworks, i.e., the composition of free thiols will influence, and will be influenced by, the subnetwork that is active under one particular set of conditions (acid or base). This influence was illustrated by treating a mixture of dithioacetal **52**, benzene disulfide **53** and 2-phenylethanethiol **54** with acid and base following two opposed sequences. The obtained final product distributions were different depending on the reaction sequence. When the acid-base sequence was applied (Figure 10, *Path a*), none of the dithioacetals detected in the final mixture (**55** and **56**) included the phenylthio moiety in their structures. This is because at the time the dithioacetals are exchanged, the phenylthio unit is part of disulfide **53**, and as such is unreactive. On the contrary, when the opposite sequence is applied (Figure 10, *Path b*) the phenylthio unit is incorporated into the final dithioacetals **62** and **63** since the corresponding thiophenol (**60**) is produced from **53** during the preceding disulfide exchange step. For the same reason that **62** and **63** are exclusive products of *Path b*, disulfide **61** is observed only when *Path a* is followed.

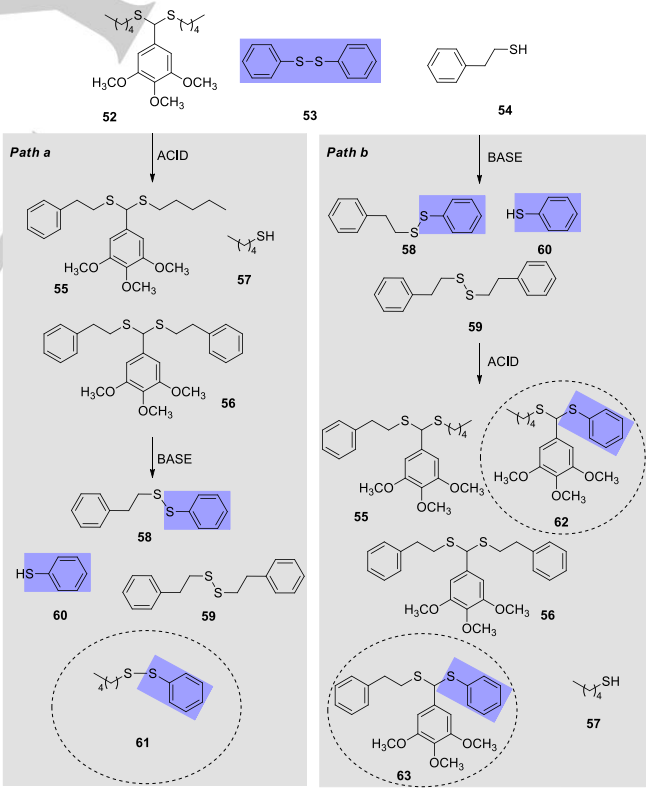

Figure 10. Dynamic system of communicating and sequential reactions. Solution of dithioacetal **52**, disulfide **53**, and thiol **54** in $CHCl_3$ after the addition of TFA, followed by the addition of piperidine (***Path a***), or first piperidine and then TFA (***Path b***).

This type of dynamic systems built around simultaneous-communicating reactions can be represented as a two-layer network wherein each layer is produced by a given reaction condition. Therefore a change in the reaction conditions is translated into a change in the network wiring (Figure 11a). This concept was further extended by using irradiation to activate both reactions simultaneously. Under such conditions, a fully wired network is produced (Figure 11b).[31]

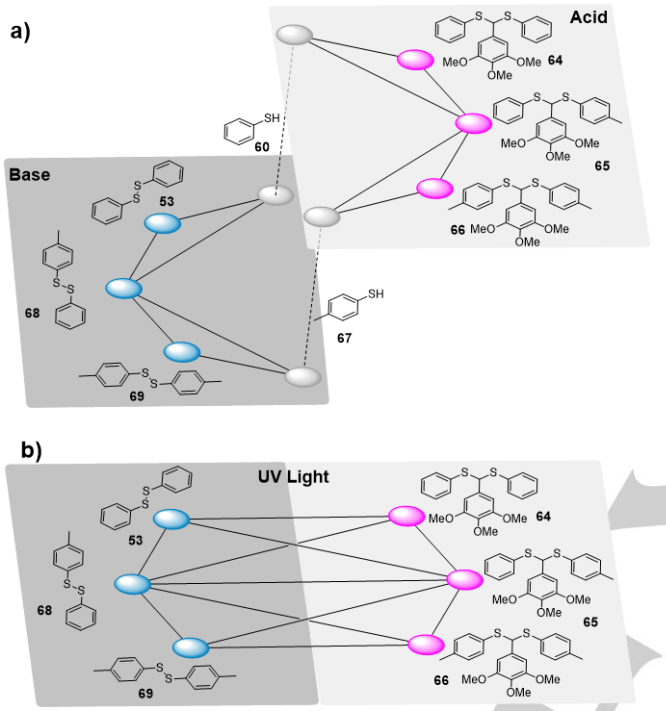

Figure 11. Network rewiring in a dynamic chemical system. Each subnetwork can be individually (TFA or TEA, CH_3CN) (a) or simultaneously (UV 365 nm, 9,10-dicyanoanthracene, O_2, CH_3CN) (b) activated.

Multilevel dynamic systems based in Orthogonal and Communicating Reactions

The combination of orthogonal and communicating reactions in the same system opens new opportunities; however, examples of such combinations are very rare. We have combined hydrazones, disulfides and thioesters in one single dynamic system. In this design, disulfides and thioesters can communicate with each other, whereas both are orthogonal to hydrazones.[43] The combination of these three reactions was later used to search and improve a receptor that binds Li^+. Starting from building block **70**, hydrazone chemistry was used to generate a dynamic mixture of macrocycles of different size that in the presence of LiBr favored the formation of the trimer (Figure 12). Once the macrocycle size was fixed, the exchange of disulfides and thioesters was activated to search for side chains in an orthogonal chemical space. The presence of the template LiBr led to the amplification of one macrobicycle containing an intramolecular disulfide bond (**71**), product of disulfide exchange, and a macrocycle with different side chains (**72**), produced by thioester exchange (Figure 12). The ratio of the complexes detected by electrospray ionization-mass spectrometry indicated that the receptors **71** and **72,** generated on the second level, possess a stronger preference for LiBr than its precursor.

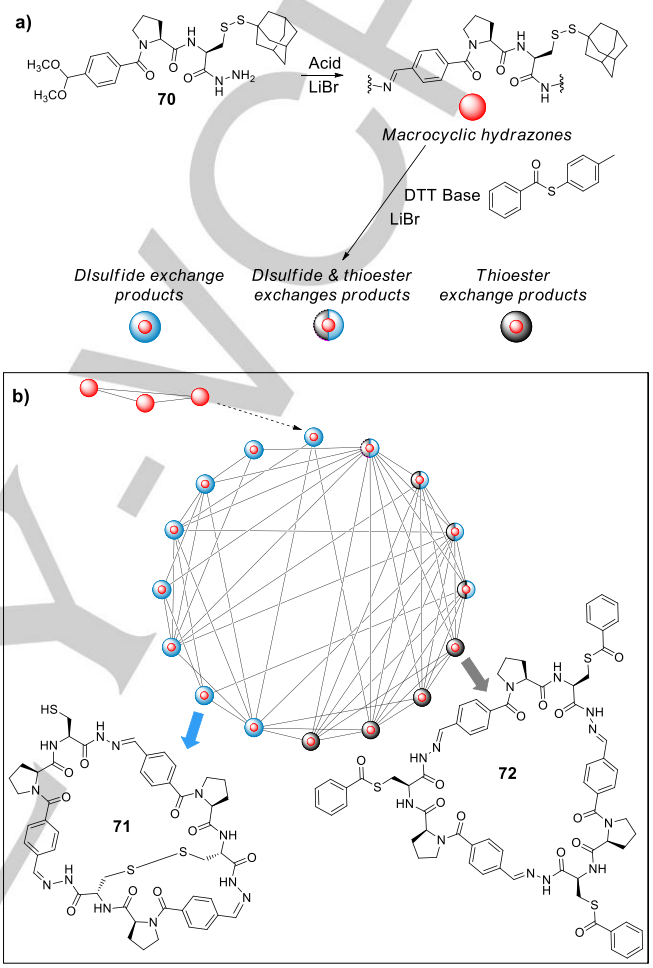

Figure 12. Combination of hydrazone, disulfide and thioester exchanges, (a) Hydrazone exchange is used for size selection ($CHCl_3$/MeOH 98:2, TFA) whereas disulfide and thioester exchange ($CHCl_3$/MeOH 98:2, TEA) are applied for sidechain selection. (b) Molecular network describing the mixture obtained through hydrazone exchange (red nodes) or disulfide and thioester exchanges. Molecular structures of the amplified macrocycles

Conclusions

Adaptive chemistry has been defined as “the chemistry exploring the response of a system to physical or chemical agents”.[32] Such responsiveness involves changes at the supramolecular and/or molecular levels. Adaptation at the molecular level involves formation and breaking of covalent bonds through reversible reactions. Systems that include more than one reversible reaction have properties that depend on the reactions relative reactivity.

When the reactions are orthogonal, independent molecular subnetworks can be generated. This combination of reactions has been used for the spatially organized decoration of peptide scaffolds and the construction of multicomponent surface architectures. The chemical composition of surfaces is fundamental to determine properties in the nanoscale. The dynamic covalent exchange has been applied for the tuning of nanoparticle interfacial properties.[33,34] The combination of orthogonal reactions could enhance the potential of this approach.

The use of dynamic covalent chemistry has led to the preparation of responsive polymer materials with a variety of properties.[35-39] Although some polymers based in two orthogonal reversible reactions have been reported,[40-42] multi-responsive systems based in the combination of several reversible reactions have not been investigated.

The combination of two reversible reactions that can communicate with each other endows the system with particular properties. Since both reactions share one building block type, whilst one exchange pool grows, the other has to shrink, making these two exchange chemistries antiparallel.[24] So in principle, this type of dynamic system can be biased toward the desired connectivity type by external agents.

When a sequence of reversible reactions is possible, the chemical compositions reached after successive equilibriums represent a recording of the historical contingencies that can be sensed by the adaptive capacity of the system. If the subnetworks produced by the different reversible reactions are connected, the succession of equilibrium states introduces the time dimension and configures the particular history of the system. In this manner, differences in the final composition may be originated during the inactivation of a previous level of exchange. At any time, the process contains information that is potentially useful to trace the particular sequence of significant chemical events that affected the composition of the system up to that moment. As these landmarks, represented by some molecular features of the components, remain fixed, exploratory and evolutionary properties can be conferred to the system. This combination of sequential adaptation-fixation steps remains almost unexplored.[43]

An important part of systems chemistry seeks to develop novel reaction networks from the integration of simple elements in order to comprehend, design and to exploit complex behaviour in chemical systems.[44] Examples discused along the manuscript show that both the power of dynamic combinatorial chemistry and the selective wiring between structures can help to generate unprecedented dynamic multilevel systems. Given the relevance of dynamic combinatorial chemistry to generate reaction networks, it can be expected that combining reactions with different properties in terms of relative reactivity will become a useful tool to generate dynamic systems with desired functions. A few interesting reversible reactions have been recently introduced in the field.[45] However methodological advances are required in order to fully exploit the reactions interdependence in multilevel systems. Very recently, You *el at.* introduced an interesting strategy to control dual reactivity in dynamic covalent chemistry.[46] Such type of approach will allow the preparation of tunable multireaction networks wherein different reaction pathways can be induced.

Systems chemistry seems to be the natural habitat where the exciting field of complex multilevel systems is burgeoning. Probably in the next future, different fields of research within the wide area of systems chemistry can be benefited from combining different reversible reactions in the same system.

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Keywords: molecular network • dynamic covalent • sequential • orthogonal • communicating

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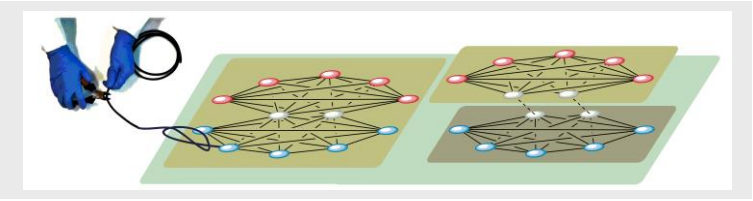

Molecular networks of dynamic multilevel systems can exhibit different connectivities between nodes. In this concept, different molecular networks from synthetic systems are discussed which can be produced by combinations of different reaction types

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